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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/848,353	05/04/2001	James M. Staddon	0623.0410001/EKS/BJD	1015

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

8M-

Office Action Summary	Application No.	Applicant(s)	
	09/848,353	STADDON ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 January 1939*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) *1 and 26-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1,21-39 are pending.

Response to restriction requirement filed 02/18/2004 is acknowledged. Applicant elected, without traverse, Group II, claims 21-26. Claims 1, 27-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected groups. Cancellation of claims 1, 27-39 is requested.

In response to election of species requirement, applicant elected pervanadate as species of agent effecting tyrosine kinase phosphorylation. Claims reading on the elected species are 21-25. Claim 26 is withdrawn from consideration as drawn to non-elected species.

Claim Objections

2. Claim 21 is objected because of the use of the term "the permeability". The term has not been defined before, therefore, the article "the" should be removed.

Claim Rejections - 35 U.S.C. § 112, second paragraph.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "subject in need of reducing permeability of physiological barrier" in claim 21 is vague and indefinite. It is not clear which subject is in need of "increasing permeability of physiological barrier".The specification, although providing particular examples, does not provide a standard for ascertaining the requisite conditions.

Claim Rejections - 35 U.S.C. § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 21-25 are rejected under 35 U.S.C. 102(a) as anticipated by Shisheva et al. (DN PubMed ID: 8275968 Endocrinology, (1994 Jan) 134 (1) 507-10), and as evidenced by Shisheva and Volberg and Hilsted and McRoberts.

Shisheva et al reference describes *in vivo* administration of pervanadate, an inhibitor of tyrosine phosphatase and a potent insulinomimetic, which results in lowering blood glucose level. The reference does not specifically teach alteration in permeability of physiological barrier. However, such effect would be inherent because pervanadate is known to affect permeability of physiological barriers. Thus, Shisheva et al. (Database Medline, DN PubMed ID: 8404595 Endocrinology, (1993 Oct) 133 (4) 1562-8). teaches that pervanadate increases cell permeability to glucose; Volberg et al. (1992, see IDS) teaches that pervanadate elicits tyrosine phosphorylation of proteins at the adherens junction. Further, pervanadate is a potent insulinomimetic, and insulin is known to increase permeability of various physiological barriers. See for

example, Hilsted et al. (Database Medline, PubMed ID: 1547928 Diabetologia, (1992 Feb) 35 (2) 99-103) or McRoberts et al. (Database Medline, PubMed ID: 2156894 Journal of clinical investigation, (1990 Apr) 85 (4) 1127-34). Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02.

6. Claims 21-25 are rejected under 35 U.S.C. 103(a) as obvious over Teshima et al. (Database MEDLINE, DN PubMed ID: 7524478. Stimulatory effect of pervanadate on calcium signals and histamine secretion of RBL-2H3 cells. Biochemical Journal, (1994 Sep 15) 302 (Pt 3) 867-74.)

The reference teaches that pervanadate, which is inhibitor of tyrosine phosphatase, induced Ca2+ entry from the external medium which resulted in cell activation, secretion of histamine, IP3 formation, and sustained increase in [Ca2+]i. The increase of Ca2+ entry from the external medium across cellular membrane is considered as increase in permeability of physiological barrier (cell membrane) to Ca2+. As cell

activation is a desired effect in plurality of disorders, it would have been prima facie obvious to one skilled in the art at the time the invention was made to be motivated to utilize the referenced in vitro finding to achieve the correspondent in vivo effect.

Claim Rejections - 35 U.S.C. § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing permeability of kidney endothelial cells *in vitro* by inhibition of tyrosine dephosphorylation, does not reasonably provide enablement for an *in vivo* increase of permeability of any physiological barrier caused by any agent capable of reducing tyrosine dephosphorylation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The standards by which a specification is judged to be "enabling"were set forth in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988). Some of the standards taken under consideration are: 1) the state of the prior art; 2) the predictability or lack thereof in the art; 3) the amount of direction or guidance present; 4) the presence or absence of working examples; and 5) the breadth of the claims. The following is an analysis of some of these factors in relation to this application.

The breadth of the claims

The instant invention is drawn to method for decrease in permeability of physiological barrier. The breadth of the claims encompasses any physiological barrier in any tissue. Such breadth encompasses practically any interface existing in a living organism, from bones , and skin, and, e.g., cornea, to any cellular and intracellular membranes.

The state of the art and predictability of the prior art.

The prior art teaches that, even if limited to one certain type of physiological barrier, the properties of the physiological barrier vary substantially. For example, for endothelial barrier, Lum (Can. J. Physiol. Pharmacol., 74, 787-800, 1996; see IDS) teaches that transendothelial permeability differs not only between organs but also between parts of the same organ (p. 793, last paragraph). Moreover, an immense

diversity of properties of a plethora of physiological barriers located in a living organism is fully recognized in the art. For example, regulation of properties of cells by kinases, most prominently, protein kinase C and tyrosine kinase, vary from one cell type to another and a mechanism of regulation found in one type of cells is often not operable or have an opposite effect in another cell type. In particular, in regard to putative regulation of permeability by tyrosine (de)phosphorylation, the art demonstrates possibilities of regulation in all possible directions or lack thereof: Mullin et al (Am. J. Physiol. 263:F915-F924, 1992; see IDS) teach that inhibition of tyrosine phosphorylation reduces permeability of epithelial gap junction; however, such effect is observed only on the top of preceding stimulation of tyrosine phosphorylation, whereas tyrosine kinase inhibitor alone fails to elicit any change in permeability. On the other hand, there are multiple observations implying that inhibition of tyrosine kinase increases permeability of a barrier. For example, Volberg et al. (EMBO Journal, 11, 1733-1742, 1992; see IDS) teaches that inhibition of tyrosine kinase activity in adherens-type junctions recovers adherence junction deteriorated by overexpression of tyrosine kinase in the tissue, and thus restores, rather then reduces (as would be expected according to the instant invention) permeability of the junction. Filson et al. (Cell Growth and Differentiation. 1 (12) 661-8, 1990; see IDS) teaches that a loss of gap junction permeability correlates with increase in phosphorylation of tyrosine. Crow

(Oncogene, 7 , 999-1003, 1992; see IDS) and Swenson (Cell Regulation, 1, 989-1002, 12/1990; see IDS) teach that phosphorylation on tyrosine is involved in disruption of gap junctional communication (see Abstracts), and hence results in decrease, rather than increase, in its permeability. Therefore, art is not predictable in regard to the effect of tyrosine phosphorylation/dephosphorylation on a physiological barrier permeability. See, e.g. Lum et al. (Can. J. Physiol. Pharmacol., 74, 787-800, 1996; see IDS) who teaches that contribution of tyrosine kinases in mediating increased vascular permeability remains unclear (p. 796, second paragraph).

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. In

applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as physiological activity, more may be required. MPEP 2164.03.

The presence or absence of working examples and guidance in the specification

The examples in specification demonstrate several effects caused by pervanadate and phenylarsine oxide in MDCK cells: increase in tyrosine phosphorylation decrease in the transcellular electrical resistance (and by implication increase permeability)and increase in the paracellular flux of sucrose. There are no examples on use of pervanadate *in vivo.* There are no working examples, nor guidance present in the specification in regard to achieving in vivo effect of increase of permeability in any other type of physiological barrier and by any agent that inhibits tyrosine phosphatase. The specification does not provide any dosage range for achieving increase in permeability of a physiological barrier when administered to a subject, there is no standard by which to measure whether the compound will operate *in vivo* as intended. Further, there are no guidelines for determination of dosage needed to provide increase of permeability in one barrier (e.g., epithelial) as compared to another barrier, e.g., skin. Further, there are no guidelines how to select a subject who is in need of increase in

permeability of (which?) barrier. Additionally, the metes and bounds of the scope of physiological barriers is extensive. As discussed above, the art is such that random selections of agents that may, directly or indirectly, increase tyrosine phosphorylation and/or their doses will not be effective in the treatment of different disease states which require reduction in tyrosine phosphorylation. A dosage selected at random is likely to be completely ineffective, or to affect "healthy" barriers to the same adverse extent as the barrier in need of reducing its permeability.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art, one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Conclusion.

8. No claims are allowed

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

April 26, 2004

mlb

MICHAEL BORIN, PH.D
PRIMARY EXAMINER